

VII. INTERNATIONAL CONSIDERATIONS

A. Introduction

This chapter examines the potential impact of the rule on U.S. competitiveness in biotechnology. A description of international regulations is provided to place the TSCA biotechnology rule in the context of additional proposed and enacted legislation that may affect the industry. The remainder of this chapter addresses similarities and differences between the rule and guidelines, regulations, and legislative initiatives in other countries.

B. Effects of the Final Rule on International Competitiveness

A limited examination of selected foreign regulations suggests that no close competitor to U.S. industry would enjoy a significantly less stringent regulatory environment compared to the requirements included in the rule. Furthermore, several countries important in the world biotechnology market currently appear to have more stringent regulatory approaches than the one described in this rulemaking.

The remainder of this chapter provides a brief overview of international markets, describes several foreign biotechnology regulatory approaches, and mentions some theoretical considerations in analyzing effects of the rule on international competitiveness.

1. Overview of International TSCA Biotechnology Markets

Biotechnology is an international industry, and TSCA-type biotechnology applications are no exception. Countries with large numbers of biotechnology companies include the United Kingdom, Japan, Canada, France, and Germany.* Even though it lacks large numbers of biotechnology firms, Switzerland is considered a major biotechnology player through its industrial,

* These five countries, along with U.S., are the leading contributors to biotechnology worldwide (Bioscan 1989).

chemical and pharmaceutical industries, such as Ciba-Geigy, Hoffman-LaRoche, and Sandoz. Similarly, Novo-Nordisk and Gist Brocades, leading enzyme manufacturers in Denmark and the Netherlands, make these countries important to TSCA biotechnology markets.

The trans-national nature of one major TSCA biotechnology market, the detergent enzyme industry, is illustrated by a recombinant microorganism developed by Novo-Nordisk. The microorganism produces a fat-degrading enzyme used in laundry detergents, first isolated by Novo's Japanese subsidiary. The microorganism was sent to Denmark for further development, then back to Japan for production at a Novo plant. The enzyme product itself was shipped to Denmark for granulation, then back to Japan for sale to a Japanese detergent maker. The Japanese plant also produced enzyme products for export to other Asian markets.

Other microorganisms or products of microorganisms in TSCA applications are also traded globally. These include the commodity chemicals citric acid, xanthan gum, fuel ethanol, and lactic acid; and microorganisms for environmental applications such as waste treatment (Krupka 1989) and nitrogen fixation (Smith 1990).

2. International Regulation of TSCA Biotechnology Markets

It was not feasible to comprehensively examine the regulatory situation for biotechnology in each country. However, this section provides highlights for several countries and international organizations.

All major countries involved in the development of industrial biotechnology appear to have some form of government oversight of genetically modified microorganisms for both research and development (R&D) and general commercial use, as the following examples illustrate:

- Denmark's relatively restrictive "Environment and Gene Technology Act" prohibits releases except with special government approval. While a genetically modified plant was recently approved for release, there have been no officially sanctioned releases of genetically modified microorganisms. Denmark agreed to adopt European Community (EC) directives on genetically modified organisms. (Denmark 1986, Dixon 1989c).
- Germany has also prohibited releases except under special circumstances (Gibbs 1987). At least one field test of a genetically modified plant (petunia) has been conducted. Contained as well as released uses of engineered microorganisms have been held up by lack of a law permitting use of genetic technology (Hodgson 1990a, Biotechnology 1989). However, a new Germany "Gene Law" has been in place since July 1990 (USDA 1990).
- In the Netherlands, the 1985 Chemical Substance Act was revised to cover genetically modified organisms (Hodgson 1990b).
- UK regulations which came into force in 1989 introduced mandatory notification of the use of genetically manipulated organisms and of their intentional introduction into the environment (Ashford 1990).
- In France, a biosafety review committee under the Ministry of Agriculture reviews and approves all field tests (USDA 1990, France 1987).
- The Organization for Economic Cooperation and Development (OECD) has developed scientific principles for safety assessment for large scale contained applications (OECD 1986), and for field experiments (OECD 1990). While OECD has no regulatory authority, its work influences the practices of the major industrialized countries (Royal Commission 1989).

The following sections discuss comparable biotechnology regulations affecting TSCA-type applications in the European Community, Japan, and Canada.

a. European Community (EC)

At the time of this report, the European Community (EC) was comprised of twelve nations* that sought to establish a single internal market by 1992 (IBA 1989). The European leaders in biotechnology are EC members, including the UK, France, Germany, Denmark, and the Netherlands.

* At the time of the report, the EC consisted of the following countries: United Kingdom, France, Germany, Denmark, the Netherlands, Belgium, Greece, Ireland, Italy, Luxembourg, Portugal, and Spain.

The EC has proposed several Directives affecting genetically modified microorganisms, including two that have been adopted on contained uses and another on deliberate releases (CEC 1989a, 1989b, Ashford 1990, Hodgson 1992). These EC directives are binding only as to the result to be achieved; the exact method of implementation is provided in member nation legislation (IBC 1990). Because of this flexibility, a discussion of EC directives provides general insight into regulatory trends, but may not capture differences in stringency among member nations.

i. Microorganisms Subject to Regulation

The Directives cover microorganisms whose genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. Genetically modified organisms would include microorganisms modified using techniques such as recombinant DNA, microinjection, microencapsulation, and cell fusion by methods that do not occur naturally, but would exempt microbial products developed using methods such as conjugation, transformation, transduction, and mutagenesis (CEC 1989a, 1989b).

ii. Contained Applications

The Directive on contained uses addresses both small and large scale applications of Genetically Modified Microorganisms (GMMOs). Notifications can be triggered by the use of facilities for the first time for operations involving contained fermentation and/or new microorganisms subject to the Directive. Notification requirements vary depending on the risk of the microorganism and the type of operation. The requirements are summarized in Table VII-1.

As shown in the table, the requirements depend on the type of operation (e.g., teaching, research, non-commercial, commercial), scale (e.g. less than

ten liters, more than ten liters), and the risk category of the subject microorganism.

One difference between U.S. and EC approaches is that the EC approach requires advanced notification for some contained R&D applications. Another potential difference is that, unlike the U.S. rule under TSCA, risk categories in EC member state rules may not be defined by species or strain of recipient organism, so that the number of organisms qualifying as low risk under the EC approach could be more or less than under U.S. regulation. The criteria used to determine notification requirements under the Directive, however, are similar to those under the rule.

iii. Environmental Applications

Regulation would be more stringent for released genetically modified organisms than for contained uses. An R&D release would require case-by-case approval by the national government, with an expected review period of up to 90 days and provision for comments by other member countries (CEC 1989b). A commercial application also would require prior approval by the government of the country where the product is to be marketed. Following this approval, other member nations would have up to 60 days to object to a commercial-level environmental application (CEC 1989b). As under TSCA, requests for more information could lead to longer review periods.

It is difficult to project actual differences between U.S. and EC reviews at the R&D level, since there is flexibility in review periods and information requirements under both systems, and since similar scientific concerns are likely to drive these reviews. The U.S. review could be somewhat less burdensome, however, because submissions would be reviewed by only one national government, because oversight of contained R&D would be reduced, and because review periods would be shorter. In addition, the U.S. Department of

Table VII-1. EC Proposed Reporting

<u>Proposed Reporting for Contained Applications</u>		
•	First use of particular installation for Group I GMMOs	- prior notification - use after 90 days if not prohibited
•	First use of particular installation for Group II GMMOs	- prior notification - explicit consent required - CA decides within 90 days
•	Type A use of Group I GMMOs under 10 liters in previously approved installation	- no notification required - records must be kept
•	Type A use of Group I GMMOs over 10 liters or Group II GMMOs under 10 liters in previously approved installation	- prior notification - use after 60 days if not prohibited
•	Type B use of Group II GMMOs over 10 liters in previously approved installation	- prior notification - explicit consent required - CA decides within 90 days
<u>Proposed Reporting for Deliberate Release</u>		
•	Releases for R&D Purposes	- prior notification - explicit consent required of CA in relevant member state - CA decides within 90 days
•	Marketing of GMMOs	- prior notification - notified CA decides within 90 days, then sends dossier to other CAs for 60 day review - explicit consent required of CA to whom notified; any CA may raise objections; if the CAs cannot reach agreement, the Commission decides

Note: GMMO = Genetically Modified Microorganism.
CA = Competent [regulatory or review] Authority of Member State.
Type A = Small scale research.
Type B = Other activities.
Group I = Lower Risk
Group II = Higher Risk

Source: Ashford 1990.

State suggests that delays may occur in the event of a conflict between a member state and a competent authority (CA). Member states have the ability to put a hold on product use in another state, and even relatively short delays of weeks or months may cause the growing season to be missed, causing delays in product testing or commercialization by more than a year. In addition, the Commission's review, which is responsible for resolving these disputes, is not subject to a time constraint, implying that their review could continue indefinitely. Nevertheless, to date, at least 143 field tests of genetically modified plants have taken place in 9 EC countries (EC 1993, Hodgson 1992).

b. Japan

Japan is considered a strong competitor in world biotechnology markets (Dibner 1987). Detergent enzyme production in Japan using a recombinant microorganism was described earlier. Other areas of Japanese activity involving TSCA jurisdiction applications include research into recombinant microorganisms for toxic waste treatment and mining (Biotechnology 1989).

Japan controls rDNA activities through government guidelines. These guidelines do not have the force of law. However, they are accepted as binding by Japanese industry, and there is an informal system of financial and social constraints to which industry and laboratories are sensitive (Ashford 1990).

Five Japanese governmental bodies have promulgated biotechnology guidelines for contained uses relevant to TSCA-type applications: the Ministry of Education; the Science and Technology Agency; the Ministry of International Trade and Industry (MITI), which promotes biotechnology in the chemical

industry; the Ministry of Health and Welfare; and the Ministry of Agriculture, Forestry and Fisheries (MAFF) (Ashford 1990, OECD 1989).

i. Microorganisms Subject to Regulation

The guidelines cover only organisms modified by recombinant DNA as defined by the NIH guidelines. They do not cover manipulations such as cell fusion, microinjection, protoplast fusion, gene deletion, transformation, transduction, random mutagenesis, nor do they cover naturally-occurring microorganisms (OECD 1989).

ii. Laboratory Research

Guidelines for recombinant DNA research generally follow OECD guidelines, but have added requirements for minimization of releases in exhaust gases, and inactivation of liquid wastes by validated means (OECD 1990). As with U.S. NIH guidelines, there is no general notification requirement. However, certain types of experiments -- including those involving deliberate release -- are to be conducted "under the direction of the government."

iii. Large Scale Contained Applications

The two agencies concerned with TSCA-type industrial applications, MITI and MAFF, have issued guidelines for commercial-scale contained use of recombinant DNA microorganisms. The guidelines follow OECD recommendations (MITI 1986, MAFF 1986, OECD 1986).^{*} Compliance is voluntary, but a company can request government review of its production facilities and procedures (Ashford 1990, MAFF 1986). MITI has approved at least 88

^{*} The MAFF guidelines became effective in early 1989, and a third set of guidelines from the Ministry of Health and Welfare covers food and drug production.

applications for "large scale"* work -- 87 at GILSP (Good Industrial Large Scale Practice -- the minimum OECD containment level), and one at the higher Category 1 level. The following microorganisms were involved (OECD 1989):

<u>E. coli</u> strain K 12	83
<u>Bacillus amyloliquefaciens</u>	3
<u>Providencia stuartii</u>	1 (containment Category 1)
<u>Bacillus stearothermophilus</u>	1
<u>Aspergillus oryzae</u>	1

Approval for production of detergent enzymes using the Novo-Nordisk microorganism required three or four months (Novo 1989, Chemical Week 1988), suggesting that the approval process may be comparable in length to the U.S. PMN review period.

iv. Released Applications

As of May 1989, no recombinant DNA microorganisms had been introduced into the environment in connection with either research or commercial-scale use in Japan (OECD 1989). Three sets of current or expected guidelines are relevant to environmental applications in TSCA-type application areas.

First, the laboratory research guidelines mentioned above call for experiments to be conducted "under the direction of the government" (Ashford 1990).

Second, the 1986 MAFF guidelines for agricultural industries address deliberate release as well as contained use. Before release to the open environment, the organism would have to be evaluated in a "simulated model environment" that apparently could include outdoor sites with appropriate confinement measures (MAFF 1986). The evaluation would be conducted by the company itself. The version of the guidelines available for this analysis did

* The cutoff for large scale was not given, and it was not determined for this analysis whether the 88 applications include R&D uses. In the Science and Technology Agency guidelines, "large scale" means over 20 liters (Ashford 1990).

not state whether such a release would also involve government review. The MAFF guidelines for field testing of genetically engineered plants were finalized in 1989 (Martin 1989).

c. Canada

Canada is active in biotechnology* and the government is promoting TSCA-type applications such as nitrogen fixation, cellulose utilization and waste treatment, mineral leaching, and metals recovery (OECD 1989). There have not yet been any environmental introductions of living recombinant microorganisms, but plasmid-cured and transconjugant Bacillus thuringiensis strains have been field tested (Ashford 1990). Information was not obtained concerning uses of genetically engineered microorganisms in contained structures.

In 1988, Canada passed the TSCA-like Canadian Environmental Protection Act (CEPA) (Environment Canada 1988a, 1988b). As with TSCA, the new Act regulates chemicals not covered by food, drug, or pesticides legislation. The Act is applicable to microorganisms, and draft regulations included all microorganisms. Provisions for exemption from review (waivers) are also in the draft regulations.

3. Impacts of TSCA Regulations on International Competitiveness

A considerable amount of further research would be required to determine fully the impacts of the rule on the international competitiveness of U.S. biotechnology firms. However, several preliminary observations can be made.

First, any moderate effects of the rule on industry cost -- positive or negative -- could be overwhelmed by other technical, economic and legal

* The 1989 BioScan directory listed Canada as having 46 biotechnology companies (compared with roughly 60 each for Japan and the UK) (BioScan 1989).

forces affecting international competitiveness. For example, the following factors are thought to be important to biotechnology competitiveness (Simpson 1990, Fairtlough 1990):

- the level of basic molecular biology and related sciences and engineering disciplines; this is affected by the quality of universities and their interactions with businesses among other things;
- national policies that affect the promotion and funding of biotechnology research;
- the availability of venture capital or other financing for high-technology start-ups;
- the nature of patent protection.

Second, while it was not possible to project impacts of the rule on U.S. research and innovation (see Chapter VI), in theory, any negative impacts on innovation at home could also affect the U.S. international position. This could occur even if the U.S. regulations were less stringent than foreign regulations -- perhaps appearing as a reduction in a U.S. advantage rather than as a disadvantage. However, any such negative impacts might be partly mitigated by gains in other biotechnology fields (e.g., medical, animal health, or plant biotechnology) if company or university resources were diverted away from TSCA applications and into other areas of biotechnology research. Conversely, any encouragement of innovation due to the rule would tend to help the U.S. competitive position.

Third, it is difficult to draw precise conclusions concerning the relative stringency of various national regulations, because the regulatory frameworks in leading biotechnology countries are in a state of transition, because few microorganisms have been reviewed, and because the current and proposed regulatory language of the foreign oversight programs does not fully capture the actual stringency of requirements when put into practice. Actual requirements may depend, to some extent, on local social, economic, and

political factors as well as the actual regulatory language and scientific considerations. Overall, the similarities among stated national regulatory approaches examined for this RIA were more striking than the differences, and truly significant differences may not become apparent until there have been several years of experience with the various regulatory schemes.

To a great extent, the scientific knowledge base concerning microbial ecology is international, and public concerns about risks of genetically modified organisms are shared worldwide. These shared concerns have prompted a global rethinking of biotechnology regulation, with considerable exchange of information and viewpoints among countries. For example, the U.S. and EC have held talks as part of their Bilateral Consultation on Environment which have addressed technical issues in biotechnology regulation. A principle aim of these discussions is the development of mutually acceptable data and information in the area of biotechnology risk assessment. In addition, efforts have been ongoing in OECD since the mid-1980s to develop harmonized approaches on safety in biotechnology.

These efforts internationally have resulted in increased harmonization of the approach that various countries take toward the risk presented by biotechnology products. Future work could involve the development of guidelines for test data and protocols and further exchange of information. This activity could lead to a convergence of regulatory positions among the countries most active in TSCA biotechnology markets.